EVALUATION OF ANTI-GOUT POTENTIAL OF SELECTED MALAYSIAN MEDICINAL PLANTS

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DEDICATION

Dedicated to: My late father, Abu Bakar Talib, my mother, Suriyah Mohd Isa, My siblings, Ahmad Fikri, Fariza Ilyani, Ahmad Faizal Afiffy (late brother) and Fazreena Aryanni, my lecturers and friends for their support and encouragement over the years who understand and guided me through the journey of my study and for all who believe in me and keep whispering “You can do it”.

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ABSTRACT

Gout is a type of arthritis that causes painful inflammation in joints due to the elevation of uric acid in the blood. Allopurinol is a common drug used for treating gout. However, due to unwanted side effects, new alternatives with fewer side effects are desired. The objectives of the study are to screen the six potential Malaysian medicinal plants for anti-gout activity using *in vitro* enzyme assay; to optimize the extraction conditions of the three selected plants using response surface methodology (RSM); to determine the cell viability of the three extracts towards RAW 264.7 murine macrophage cell line; to investigate the *in vivo* anti-gout mechanism of three selected plants; and to profile the bioactive compounds present in the three selected plant extracts. Six selected plants were screened for their anti-gout activity *in vitro* of which three plants (i.e *Euphorbia hirta, Strobilanthes crispa* and *Christia vespertilionis*) were further analyzed for their optimum extraction conditions using RSM. The effects of the plant extracts on the serum uric acid levels in hyperuricemic rats were then evaluated and lastly the bioactive compounds of the plant extracts were analyzed using liquid chromatography-mass spectrometry (LC-MS). *E. hirta, S. crispa* and *C. vespertilionis* exhibited XO inhibitory activity *in vitro* with more than 60 % at 100 µg/mL. Findings showed that the optimum extraction conditions of phytochemical compounds and anti-gout activity of these plants were at temperature of 65.09-79.07 °C for 5.0-17.42 min with solid to liquid ratio of 1:17.33-1:20 g/mL, respectively. *C. vespertilionis* displayed less cytotoxic against RAW264.7 cells as compared to *S. crispa* and *E. hirta*. For the *in vivo* study, the treatment of the hyperuricemic rats with 200 mg/kg of *E. hirta*, *S. crispa* and *C. vespertilionis* extracts reduced the serum uric acid levels significantly by more than 40 % as compared to hyperuricemic rats. The LC-MS analysis also revealed the presence of phytochemicals such as flavonoid and phenolic compounds in the plant extracts which might be associated with the anti-gout activity. Hence, this study clearly demonstrated that *E. hirta, S. crispa* and *C. vespertilionis* aqueous extracts are potential as anti-gout agents.

ABSTRAK

Gout adalah sejenis arthritis yang menyebabkan keradangan yang menyakitkan di sendi disebabkan oleh peningkatan asid urik dalam darah. Allopurinol ialah ubat yang biasa digunakan untuk merawat gout. Walau bagaimanapun, disebabkan kesan sampingan yang tidak diingini, alternatif baru dengan kesan sampingan yang lebih sedikit adalah diperlukan. Objektif kajian ini adalah untuk mengenal pasti enam tumbuhan ubat-ubatan Malaysia yang berpotensi sebagai anti-gout dengan menggunakan enzim *in vitro*; untuk mengoptimumkan keadaan ekstraksi tiga tumbuhan terpilih dengan menggunakan kaedah permukaan respon (KSR); untuk menentukan daya maju sel tiga ekstrak terhadap sel makrofaj RAW 264.7; untuk mengkaji mekanisme aktiviti anti-gout *in vivo* oleh tiga tumbuhan terpilih; dan membuat profiling sebatian bioaktif yang terdapat di dalam tiga ekstrak tumbuhan terpilih. Enam tumbuhan yang dipilih telah dikaji untuk aktiviti anti-gout di mana tiga tumbuhan (i.e *Euphorbia hirta*, *Strobilanthes crispa* dan *Christia vespertilionis*) dianalisa lagi untuk keadaan pengekstrakan optimum menggunakan KSR. Kesan ekstrak tumbuhan pada paras asid urik dalam darah tikus kemudian dinilai dan akhirnya sebatian bioaktif ekstrak tumbuhan dianalisa menggunakan spektrometri jisim-kromatografi cecair (SJ-KC). *E. hirta*, *S. crispa* dan *C. vespertilionis* menunjukkan aktiviti perencatan XO secara *in vitro* pada kadar lebih 60 % pada kepekatan 100 μg/mL. Keputusan menunjukkan bahawa keadaan pengekstrakan optimum bagi tumbuhan ini adalah pada suhu 65.09-79.07 °C untuk 5.0-17.4 minit dengan nisbah pepejal kepada cecair 1:17.33-1:20 g/mL, masing-masing. *C. vespertilionis* menunjukkan ketoksikan yang rendah terhadap sel RAW264.7 berbanding dengan *S. crispa* dan *E. hirta*. Untuk kajian terhadap haiwan, tikus yang diberikan 200 mg/kg ekstrak *E. hirta, S. crispa* dan *C. vespertilionis* mengurangkan paras serum asid urik secara signifikan sebanyak lebih daripada 40 % berbanding tikus kawalan. Analisis SJ-KC juga mendedahkan kehadiran fitokimia seperti flavonoid dan fenolik dalam ekstrak tumbuhan yang mungkin boleh dikaitkan dengan aktiviti anti-

gout. Secara keseluruhan, kajian ini jelas menunjukkan ekstrak akueus *E. hirta*, *S. crispa* dan *C. vespertilionis* sebagai agen anti-gout yang berpotensi.

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LIST OF SYMBOLS AND ABBREVIATIONS

°C	-	Degree celcius
g	-	Gram
h	-	Hour
mg	-	Milligram
min	-	Minute
ml	-	Milliliter
µg	-	Microgram
mg/dl	-	Milligram per deciliter
mg/g	-	Milligram per g
µg/ml	-	Microgram per milliliter
µmol/l	-	Micromol per liter
µl	-	Microliter
r	-	Pearson correlation coefficient
r^2	-	Coefficient of determination
2FI	-	Two factor interaction
ACR	-	American College of Rheumatologist
$AlCl_3.6H_2O$	-	Aluminium chloride hexahydrate
ALT	-	Alanine aminotransferase
ANOVA	-	Analysis of variance
AST	-	Aspartate Aminotransferase
ATP	-	Adenosine triphosphate
BBD	-	Box-Behnken design
BSR	-	British Society of Rheumatologist
CCD	-	Central composite design
CID	-	Collision dissociation
CMC	-	Carboxymethyl cellulose
CO_2	-	Carbon dioxide

COXIBS	-	COX-2 inhibitors
COX-2	-	Cyclooxygenase 2
DMSO	-	Dimethylsulfoxide
DNA	-	Deoxyribunucleic acid
EDTA	-	Ethylenediaminetetraacetic acid
EPP	-	Entry Point Project
ETP	-	Economic transformation program
EULAR	-	European League Against Rheumatism
FAD	-	Flavin adenine dinucleotide
FDA	-	Food and Drug Administration
GAE	-	Gallic acid equivalents
GGT	-	Gamma-glutamyl transferase
GLUT9	-	Glucose transporter 9
GNI	-	Gross national income
HCl	-	Hydrochloric acid
HPLC	-	High performance liquid chromatography
IL-1β	-	Interleukin-1 beta
IL-6	-	Interleukin-6
iNOS	-	Inducible nitric oxide synthase
ISO	-	International Organization for Standardization
KCl	-	Potassium chloride
LCMS	-	Liquid chromatography mass spectrometry
MCP-1	-	Monocyte chemoattractant protein-1
MPC-SNEDDS	-	Self-nanoemulsifying drug delivery system based on morin-phospholipid complex
MRM	-	Multiple reaction monitoring
MSU	-	Monosodium urate
MTT	-	3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide
NA	-	Not available
$NaNO_2$	-	Sodium nitrite
NaOH	-	Sodium hydroxide
NIAMS	-	National Institute of Arthritis and Musculoskeletal and Skin Diseases

NKEA	-	National Key Economic Area
NLRP3	-	Nod-like receptor family pyrin domain containing 3
NMR	-	Nuclear magnetic resonance
NO	-	Nitric oxide
NSAID	-	Non-steroidal anti-inflammatory drug
OCT	-	Organic cation transporter
OCTN	-	Carnitine transporter
OECD	-	Organization for Economic Cooperation and Development
OH	-	Hydroxyl group
PBS	-	Phosphate buffered saline
PEMANDU	-	Performance Management & Delivery unit
PGE2	-	Prostaglandin E_2
PO	-	Potassium oxonate
QE	-	Quercetin equivalents
RE	-	Rutin equivalents
RNA	-	Ribonucleic acid
RPMI	-	Roswell Park Application of Technology
RSM	-	Response surface methodology
SEM	-	Standard error of mean
SLC2A9	-	Solute carrier family 2 member 9
SPSS	-	Statistical Package for the Social Sciences
TFC	-	Total flavonoid content
TNF-α	-	Tumor necrosis factor-alpha
TNF-β	-	Tumor necrosis factor-beta
TPC	-	Total phenolic content
URAT1	-	Urate transporter 1
UV	-	Ultraviolet
UV-VIS	-	Ultraviolet–visible
VEGF	-	Vascular endothelial growth factor
WHO	-	World Health Organization
XO	-	Xanthine oxidase

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